FEATURED ARTICLE

Brain imaging measurements of fibrillar amyloid-β burden, paired helical filament tau burden, and atrophy in cognitively unimpaired persons with two, one, and no copies of the *APOE* $\varepsilon 4$ allele

Valentina Ghisays[1,2] | Dhruman D. Goradia[1,2] | Hillary Protas[1,2] | Robert J. Bauer III[1,2] | Vivek Devadas[1,2] | Pierre N. Tariot[1,2,3] | Val J. Lowe[4] | David S. Knopman[5] | Ronald C. Petersen[5] | Clifford R. Jack Jr.[4] | Richard J. Caselli[2,6] | Yi Su[1,2] | Kewei Chen[1,2,3,7] | Eric M. Reiman[1,2,3,7,8]

[1]Banner Alzheimer's Institute, Phoenix, AZ, USA

[2]Arizona Alzheimer's Consortium, Phoenix, AZ, USA

[3]University of Arizona, Tucson, AZ, USA

[4]Department of Radiology, Mayo Clinic, Rochester, MN, USA

[5]Department of Neurology, Mayo Clinic, Rochester, MN, USA

[6]Mayo Clinic, Scottsdale, AZ, USA

[7]Arizona State University, Tempe, AZ, USA

[8]Translational Genomics Research Institute, Phoenix, AZ, USA

Correspondence
Eric M. Reiman, Tel: 602-839-6999; Fax: 602-839-6253.
E-mail: Eric.Reiman@bannerhealth.com

Abstract

Introduction: We previously characterized associations between brain imaging measurements of amyloid-β (Aβ) plaque burden and apolipoprotein E *(APOE)* $\varepsilon 4$ gene dose in a small number of cognitively unimpaired late-middle-aged *APOE* $\varepsilon 4$ homozygotes (HMs), heterozygotes (HTs), and noncarriers (NCs). We now characterize cross-sectional Aβ plaque, tau tangle, and cortical atrophy (neurodegeneration) measurements, classifications, and associations with age in a larger number of unimpaired HMs, HTs, and NCs over a wider age range.

Methods: We analyzed ^{11}C Pittsburgh compound B (Aβ) positron emission tomography (PET), flortaucipir (tau) PET, and volumetric magnetic resonance imaging data from 164 study participants of age 47–86 years, including 26 *APOE* $\varepsilon 4$ HMs, 48 HTs, and 90 NCs matched for age and sex.

Results: Aβ PET measurements rose, plateaued at the respective ages of 68 and 76, and then declined with age in unimpaired HM and HT groups. Compared with NCs, these two groups began to have significantly higher Aβ PET measurements at ages 62 and 70, respectively, and no longer had significantly higher measurements by ages 71 and 78, respectively. They began to have significantly higher entorhinal cortex tau PET measurements at ages 66 and 70, respectively, and no longer had significantly higher measurements by ages 74 and 78, respectively. Brain atrophy measurements tended to decline slowly with age in all three genetic groups. Their elevated tau PET

---

measurements were attributable to those with positive Aβ PET scans. 41.0%, 18.0%, and 5.0% of the 47- to 70-year-old HMs, HTs, and NCs and 25.0%, 79.0%, and 38.0% of the 71- to 86-year-old HMs, HTs, and NCs had positive Aβ PET scans, and the long-term recall memory scores are significantly higher in the older HMs than in HT and NC groups, suggesting resistance to Aβ deposition in those HMs who remained unimpaired at older ages.

Conclusions: This study provides information about Aβ plaque burden, tau tangle burden, and neurodegeneration in cognitively unimpaired persons at three levels of genetic risk for AD. Unimpaired *APOE* ε4 HMs can be studied before their 70s to evaluate the understanding of factors, processes, and interventions involved in the *predisposition* to and prevention of AD, and after their 70s, to discover factors, processes, and interventions involved in the *resilience or resistance* to and prevention of AD.

KEYWORDS

APOE, Amyloid, Tau, Neurodegeneration, PET, MRI, Biomarkers, Alzheimer's, Prevention

Alzheimer's disease (AD) is the most common form of dementia at older ages.[1,2] Neuropathologically, AD is characterized by neuritic plaques, composed of fibrillar amyloid-β (Aβ); neurofibrillary tangles, composed of paired-helical filament (PHF) tau; and synaptic and neuronal loss.[3-5]

The apolipoprotein E (*APOE*) ε4 allele is the major susceptibility gene for late-onset AD.[6,7] *APOE* ε4 gene dose (i.e., the number of ε4 alleles in a person's *APOE* genotype) is associated with a higher risk and earlier age at onset of AD biomarker changes, cognitive decline, and dementia.[8-13] For more than two decades (starting before the advent of Aβ and tau positron emission tomography [PET] methods), we (E.M.R. and R.J.C.) and our Arizona *APOE* Cohort study colleagues have been characterizing brain imaging and cognitive measurements from an ε4 homozygote (HM)–enriched, longitudinally assessed cohort of initially 47- to 68-year-old persons with two, one, and no copies of the *APOE* ε4 allele, representing three levels of genetic risk for the disease.[10,14-20] Meantime, our Mayo Clinic Rochester colleagues (R.C.P., C.R.J., and D.K.) have been characterizing brain imaging and cognitive measures in the Mayo Clinic Study of Aging from a population-based, longitudinally assessed cohort, including but not limited to cognitively unimpaired persons, who have had Aβ PET, tau PET, FDG PET, and magnetic resonance imaging (MRI) scans over a wider age range.[21-23]

We previously characterized brain imaging measurements of amyloid-β (Aβ) plaque burden in 28 cognitively unimpaired late-middle-aged (57–72 years) *APOE* ε4 HMs, heterozygotes (HTs), and noncarriers (NCs)[10] from the Arizona *APOE* Cohort. In this study, we analyzed brain imaging measurements of Aβ plaque burden (A), tau tangle burden (T), and cortical atrophy/neurodegeneration (N) in 164 unimpaired HMs, HTs, and NCs from the Arizona *APOE* and Mayo Clinic Study of Aging Rochester cohorts over a wider age range (47–86 years).

First, we characterized associations between Aβ and tau PET measurements with age in the HMs, HTs, and NCs, and we characterized the ages at which those measurements in the HM and HT groups began to be distinguished from NCs, plateaued, and were no longer distinguished from NCs. Second, we compared Aβ PET, tau PET, cortical atrophy, long-term recall memory measurements, and A/T(N) classifications[23] in the overall HM, HT, and NC groups, and we explored the possibility that observed entorhinal tau elevations in HM and HT groups were attributable to those with a positive Aβ PET scan. Finally, we conducted a *post hoc* analysis of biomarker measurements and classifications in 47–70 and 71–86 year-old subgroups, corresponding roughly to the respective ages at which Aβ PET measurements rose and declined. The subgroup analysis was intended to provide a foundation for using AD biomarkers as endophenotypes to help clarify mechanisms by which to-be-discovered resilience or resistance factors that permit certain HM and HT groups to remain cognitively unimpaired at older ages.[24-27]

1 | METHODS

1.1 | Study participants

We analyzed cross-sectional [11]C Pittsburgh compound B (PiB) PET, flortaucipir (FTP) PET, and T1-weighted MRI scans; Mini–Mental State Examination (MMSE) scores; and auditory verbal learning test (AVLT) long-term delayed recall scores from 164 cognitively unimpaired volunteers aged 47–86 years, including 26 *APOE* ε4 HMs, 48 HTs, and 90 NCs (Table 1). Participants included 15, 26, and 43 HMs, HTs, and NCs, 48–85 years old, from the Arizona *APOE* Cohort and 11, 22, and 47 HMs, HTs, and NCs, 47–86 years old, from the Mayo Clinic Study of Aging cohort, selected to optimize matching to the Arizona *APOE* Cohort for age, sex, and education. Studies were approved by the Institutional Review Boards of Banner Alzheimer's Institute and Mayo

Clinic Rochester, and the research participants provided informed consent.

APOE $\varepsilon 4$ HMs, HTs (all with the *APOE* $\varepsilon 3/\varepsilon 4$ genotype), and NCs (with the $\varepsilon 3/\varepsilon 3$ or $\varepsilon 3/\varepsilon 2$ genotype) from the Arizona *APOE* Cohort were 47–68 years old (entry-age criteria), had a reported first-degree family history of dementia, MMSE scores of 28–30, and no diagnoses of neurological or mental illnesses at time of enrollment. *APOE* genotyping was performed as described previously.[14,29,30] They have been followed up every two years with medical histories, neurological examinations, a battery of clinical ratings and neuropsychological tests, and a growing number of PET and MRI scans (initially with FDG-PET and added Aβ and tau-PET as these became available), genetic assessments, and cerebrospinal fluid and blood samples. At time of enrollment, each *APOE* $\varepsilon 4$ HM was matched to one HT and two NCs for age, sex, and educational level.[11] At the time of their PiB and FTP PET scans, they remained cognitively unimpaired and were 66 ± 8 (46–85 years old). Participants were unimpaired at the time of their cognitive assessment and only included in this analysis if they did not meet criteria for mild cognitive impairment (MCI) or dementia.

Participants from the Mayo Clinic Study of Aging cohort (Rochester) underwent equivalent clinical ratings and neuropsychological tests,[21,23,31] and included cognitively unimpaired *APOE* $\varepsilon 4$ HMs, HTs with $\varepsilon 3/\varepsilon 4$ genotype, and NCs with $\varepsilon 3/\varepsilon 3$ or $\varepsilon 2/\varepsilon 3$ genotype. Inclusion of data from these participants made it possible to optimize matching according to age, sex, and education for the present study. They were 60 ± 7 (47–68) years old at the time of their reported PiB, FTP PET, and MRI scans.

1.2 | Brain imaging

The performance sites' PiB PET, FTP PET, and volumetric T1-weighted MRI acquisition methods and scanners and study's image processing platforms, cerebral and reference regions of interest, and image analysis methods are described in Supplementary Material 1. Briefly, the Statistical Parametric Mapping 12 (SPM12) platform was used to preprocess all images, and the Mayo Clinic Adult Lifespan Template (MCALT) and its modified Automated Anatomic Labeling atlas were used to normalize coregistered MRI scans and extract PET data from regions of interest. FreeSurfer 6 was used to extract MRI measurements of cortical thickness and bilateral hippocampal-to-total intracranial volume ratios. Composite cortical-to-cerebellar crus PiB standard uptake value ratios (SUVRs), composite cortical tau, entorhinal cortex (ERC), and inferior temporal cortex (ITC)-to-cerebellar crus FTP SUVRs, and hippocampal volume ratios were used to compare Aβ plaque, tau tangle, and regional brain volumes in each genetic group. ERC FTP SUVRs were used to compare tau tangle measurements and age associations in the three groups because of its sensitivity to detect tau burden in preclinical AD and its association with memory-related cognitive testing in unimpaired participants.[5,32–34]

Cortical-to-cerebellar crus PIB SUVRs, cortical tau-to-cerebellar crus FTP SUVRs, and cortical gray matter thickness measurements were used to classify each image as positive or negative, as previously described,[28] and based on the proposed A/T(N) framework.[35] Aβ positivity was defined using PiB SUVRs ≥ 1.42 threshold, which correspond to at least moderately frequent neuritic plaques. Tau and neurodegeneration positivity were defined using cortical tau SUVR and cortical thickness thresholds >1.23 and ≤ 2.67 mm, respectively;[28] these thresholds were based on their ability to distinguish cognitively impaired patients with a positive Aβ PET scan from cognitively unimpaired young adults.[23,28]

1.3 | Statistical analysis

The three genetic groups were compared in terms of their age, sex, educational level, MMSE scores, AVLT long-term memory recall scores, brain imaging measurements and classifications, and associations with age. Statistical analyses were performed using SPSS version 23.0 (IBM-SPSS Inc., Chicago, IL). Analysis of covariance with pairwise Fisher's least significance difference comparisons or χ^2 tests were used to compare participant characteristics, clinical ratings, neuropsychological test scores, brain imaging measurements, and the proportions of participants with positive Aβ, tau, and neurodegeneration images in each genetic group. Analyses of covariance included adjustment for

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources.
2. Interpretation: This study provides information about Aβ-PET, tau-PET, and volumetric MRI measurements, their associations with age, and amyloid/tau/(neurodegeneration) classifications in a relatively large number of apolipoprotein E (*APOE*) $\varepsilon 4$ homozygotes (HMs), heterozygotes (HTs), and noncarriers (NCs) and over a relatively large middle-to-older age range. The highlighted findings complement published neuropathological studies in *APOE* $\varepsilon 4$ HMs, heterozygotes, and noncarriers, prior brain imaging and cognitive findings from the Arizona APOE Cohort, and brain imaging and biomarker studies in cognitively unimpaired research participants, most of which include fewer HMs, fewer biomarkers, and a narrower age range.
3. Future directions: Additional studies are needed to detect and track the biomarker and cognitive changes associated with *APOE* $\varepsilon 4$ gene dose at different ages, clarify the prognostic value of measurements in each of these groups, further inform the study of risk factors and prevention therapies in unimpaired HMs at younger ages, and advance the discovery of factors, mechanisms, and interventions that promote resistance or resilience to AD in HMs who remain unimpaired at older ages.

TABLE 1 Participant characteristics in cognitively unimpaired *APOE* ε4 HMs, HTs, and NCs at ages 47–86, 47–70, and 71–86

	(a) Ages 47–86				(b) Ages 47–70				(c) Ages 71–86			
	HMs, n = 26	HTs, n = 48	NCs, n = 91	P	HMs, n = 22	HTs, n = 34	NCs, n = 74	P	HMs, n = 4	HTs, n = 14	NCs, n = 16	P
Age (range)	62 ± 9 (48–86)	64 ± 9 (47–82)	63 ± 8 (50–85)	.54	59 ± 7 (48–70)	60 ± 6 (47–69)	61 ± 5 (50–70)	.51	77 ± 7 (71–86)	76 ± 3 (72–82)	75 ± 4 (71–85)	.88
Female (%)	73%	75%	74%	.97	77%	85%	75%	.45	50%	50%	69%	.54
Education	15.5 ± 2.6	15.3 ± 2.4	15.6 ± 2.0	.72	16.0 ± 1.8	14.6 ± 2.3	15.3 ± 1.9	.04[†]	12.8 ± 4.6	16.8 ± 2.1	16.9 ± 2.2	.02[§]
MMSE	29.5 ± 0.8	29.4 ± 0.9	29.4 ± 0.8	.77	29.5 ± 0.6	29.4 ± 0.9	29.4 ± 0.8	.70	30.1 ± 1.4	29.4 ± 0.9	29.4 ± 1.0	.58
Long-term recall memory[#]	10.1 ± 3.0	9.4 ± 3.4	9.5 ± 3.5[**]	.67	9.6 ± 2.7	10.4 ± 3.0	9.9 ± 3.4[**]	.59	12.4 ± 4.3	7.1 ± 3.0	8.0 ± 4.0	.04[∥]
Aβ positive[††]	39%	35%	11%	.001[*]	41%	18%	5%	2e-4[‡]	25%	79%	38%	.04[¶]
Tau positive[††]	19%	27%	20%	.59	14%	12%	18%	.72	50%	64%	31%	.19
Neurodegeneration positive[††]	8%	21%	14%	.31	5%	12%	8%	.63	25%	43%	44%	.78

NOTE. ANCOVA 2-tailed tests were used to compare continuous variables (MMSE and AVLT long-term recall memory scores adjusted for performance site, age, sex, and education), and χ^2 test for categorical variables (sex, Aβ, tau, and neurodegeneration positivity) in (a) 47- to 86-year-old, (b) 47- to 70-year-old, and (c) 71- to 86-year-old age range. Mean ± SD, and χ^2 P values are listed.

Abbreviations: Aβ, amyloid β; ANCOVA, analysis of covariance; *APOE*, apolipoprotein E; AVLT, Auditory Verbal Learning Test; HM, homozygote; HT, heterozygote; NC, noncarrier.

[*]HM & HT > NC (P ≤ .001)

[†]HM > HT

[‡]HM > HT & NC (P ≤ .06)

[§]HM < HT & NC

[∥]HM > HT & NC

[¶]HT > HM & NC (P < .05)

[#]Auditory Verbal Learning Test (AVLT) long-term recall memory scores.

[**]One NC did not have a score.

[††]Aβ, tau, and neurodegeneration-positive images were defined using cortical PiB SUVRs ≥1.42, cortical flortaucipir SUVRs >1.23, and cortical thicknesses ≤2.67 mm, as previously described.[28]

age, performance site, sex, and educational level. Linear trends were used to assess associations with *APOE* ε4 gene dose and refer to P values between .05 and .10 as "nonsignificant trends."

1.3.1 | Associations with age

Nonparametric local regression (LOESS) curves and 95% confidence intervals[36] were used to characterize a) age associations with cortical PiB SUVRs, ERC, ITC, and cortical tau FTP SUVRs, hippocampal gray matter volumes and cortical thickness in each genetic group; and b) ages at which SUVRs in the HM and HT groups began to be significantly higher than in the NCs, plateaued, and were no longer significantly higher than in the NCs (Fig. 1; Supplementary Figs. 1–2). ERC FTP SUVRs were the prioritized tau PET measurements for the reasons noted above. LOESS fitting was performed using the R software (version 3.4.1; www.r-project.org).

1.3.2 | Measurements and classifications in the overall, younger, and older age ranges

Participant characteristics, MMSE and AVLT long-term memory recall scores, brain imaging measurements, Aβ, tau, and neurodegeneration

positivity percentages, and A/T(N) classifications were compared in the overall 47- to 86-year-old age range. As noted previously, these variables were assessed *post hoc* in the younger 47- to 70-year-old and older 71- to 86-year-old age ranges, corresponding roughly to the rise and fall of Aβ PET measurements and dementia onset[24–26,37] in the HM group.

2 | RESULTS

2.1 | Participant characteristics

As shown in Table 1, *APOE* ε4 HM, HT, and NC groups did not differ significantly in age, sex, or MMSE scores in the overall, younger, and older age ranges. Although they did not differ significantly in educational level or AVLT long-term recall memory scores in the overall age range, HMs had significantly higher educational levels than HT groups in the younger age range and significantly lower educational levels but higher recall memory scores than HT and NC groups in the older age range (P < .05, adjusted for age, sex, performance site, education, Aβ positivity, and ERC tau PET measurements, uncorrected for multiple comparisons).

There were only four HMs in the unimpaired older group, which could be due to our exclusion of participants who had already become
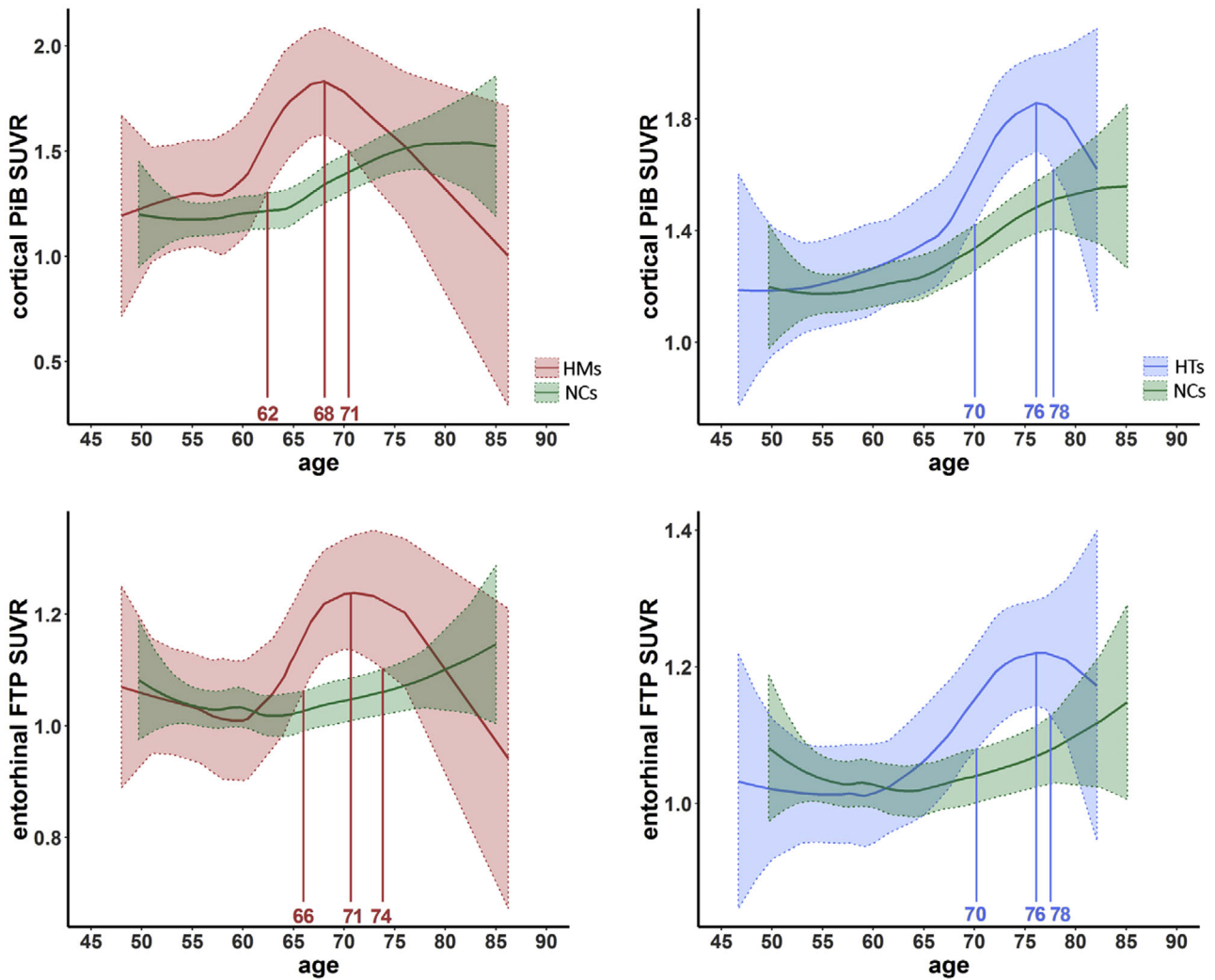
FIGURE 1 Relationships between Aβ plaque and tau tangle PET measurements and age in *APOE ε4* HMs, HTs, and NCs. LOESS-fitted curves and 95% confidence intervals for cortical PiB SUVRs and ERC FTP SUVRs in HMs versus NCs and HTs versus NCs. Ages at which these measurements in the HMs and HTs became significantly greater than in NCs, plateaued in HMs and HTs, and were no longer significantly greater than in the NCs are shown in top and bottom panels. Abbreviations: Aβ, amyloid β; HM, homozygote; HT, heterozygote; NC, noncarrier; ERC, entorhinal; FTP, flortaucipir; SUVR, standard uptake value ratio.

impaired and a historical emphasis on the enrollment of younger participants in the Arizona *APOE* Cohort, some of whom have not reached older ages. Supplementary Table 1 illustrates the potential impact of differential survivor bias on our findings: 24.0%, 9.5%, and 3.7% of initially enrolled late-middle-aged cognitively unimpaired HM, HT, and NC groups in the Arizona *APOE* Cohort who subsequently progressed to MCI due to possible AD, respectively ($P < .001$), met MCI criteria at the respective ages of 69, 75, and 77 ($P < .001$), and were excluded from this analysis.

2.2 | Associations with age

Associations between respective Aβ plaque, tau tangle, and brain atrophy measurements with age, in the *APOE ε4* HM, HT, and NC groups are shown using LOESS curves and 95% confidence intervals in Fig. 1 and

Supplementary Figures 1 and 2 (wider 95% confidence intervals at the youngest and oldest ages are at least partly due to fewer participants at those ages). In general, Aβ and tau PET measurements rose, plateaued, and declined with age in the HM and HT groups and rose more slowly in the NC group, whereas brain atrophy measurements tended to decline slowly with age in all three genetic groups.

Ages at which Aβ and tau PET measurements in the HM and HT groups began to be significantly different from NCs ("rise"), plateaued, and were no longer significantly different from NCs ("decline") and are also shown in Table 2. In HMs, cortical Aβ PET measurements began to rise at age 62, plateaued at age 68, and declined by age 71. ERC tau PET measurements began to rise at age 66, plateaued at age 71, and declined by age 74. ITC and cortical tau PET measurements plateaued at age 76 but were not significantly different from NCs at any age. HTs generally demonstrated a similar pattern, but with most rises, plateaus, and declines occurring about 4-8 years later. Their cortical Aβ and ERC

TABLE 2 Ages at brain imaging AD biomarker onset, plateau, and decline in cognitively unimpaired APOE ε4 HMs and HTs compared with NCs

Biomarker Measurement	HMs, n = 26			HTs, n = 48		
	Onset age	Plateau age	Decline age	Onset age	Plateau age	Decline age
Aβ						
Cortical PiB	62	68	71	70	76	78
Tau						
Entorhinal FTP	66	71	74	70	76	78
Inferior temporal FTP	–	76	–	70	74	77
Cortical tau	–	76	–	71	74	77
Atrophy						
Hippocampal volume	–	–	–	–	–	–
Cortical thickness	–	–	–	–	–	–

NOTE. Onset is defined by the age at which measurements began to be significantly higher than those in the NC group. Decline is defined by the age at which measurements were not longer significantly higher than in the NC groups. Estimated ages at onset, plateau and decline are likely to be influenced by differential survivor bias (i.e., the exclusion of carriers who became cognitive impaired at younger ages) and sample size (e.g., the impact of sample size on statistical significance).
Abbreviations: Aβ, amyloid β; APOE, apolipoprotein E; FTP, flortaucipir; HM, homozygote; HT, heterozygote; NC, noncarrier.

tau PET measurements began to rise at age 70, plateaued at age 76, and declined by age 78. ITC and cortical tau PET measurements began to rise at the respective ages of 70 and 71, plateaued at age 74, and declined by age 77.

2.3 | Brain imaging biomarker findings

2.3.1 | Classifications

Table 1 shows the percentages of cognitively unimpaired HM, HT, and NC groups in the overall (47–86), younger (47–70), and older (71–86 year-old) age range who were found to be Aβ, tau, and neurodegeneration-positive using their Aβ PET, tau PET, and MRI scans with the previously described criteria.[28]

2.3.2 | Aβ positivity

As shown in Table 1 and Fig. 2 (top), 39%, 35%, and 11% of HM, HT, and NC groups in the overall age range, 41%, 18%, and 5% in the younger age range, and 25%, 79%, and 38% of those in the older age range had positive Aβ PET scans, respectively. The percentage of participants with a positive Aβ PET scan was significantly associated with APOE ε4 gene dose (HM > HT > NC) in the overall and younger age ranges (linear trend, $P < .01$), but not in the older age range.

2.3.3 | Tau and neurodegeneration positivity

As shown in Table 1, the percentage of tau-positive and cortical gray matter atrophy/neurodegeneration-positive participants was not significantly different in HM, HT, and NC groups or associated with APOE ε4 gene dose in the overall, younger, and older age range.

2.3.4 | A/T(N) classifications

Table 3 shows the percentage of cognitively unimpaired participants with each of the eight proposed A/T(N) research framework classifications. Although none of the HMs in any age range were A+T+(N)+, 12%, 10%, and 2% of HM, HT, and NC groups in the overall age range and 9%, 3%, and 0% in the younger age range met A/T(N) criteria for AD (i.e., A+T+ irrespective of their N classification), and 27%, 13%, and 6% (overall age range) and 32%, 12%, and 3% (younger age range) met criteria for "AD pathologic change" (i.e., A+T–(N)–), respectively. Thus, the percentage of participants who met A/T(N) criteria for AD and AD pathologic change were each associated with APOE ε4 gene dose (HM > HT > NC) in the overall and younger age ranges (linear trend, $P < .05$), but not in the older age range. Conversely, the percentage of A–T–(N)– participants was lower in HMs than in NCs, inversely associated with APOE ε4 gene dose (HM < HT < NC) in the younger age range (linear trend, $P < .05$), and significantly lower in older than younger participants (attributable to HTs and NCs, $P < .01$, but did not reach significance for HMs).

2.3.5 | Measurements

Table 4 shows PiB PET measurements of cortical Aβ plaque burden, FTP PET measurements of the ERC, ITC, and cortical tau/tangle burden, and MRI measurements of cortical gray matter and hippocampal atrophy in HMs, HTs, and NCs from the overall, younger, and older age ranges.

2.3.6 | PiB PET measurements of Aβ plaque burden

As shown in Table 4 and Fig. 2 (bottom), HM and HT groups had significantly higher cortical PiB SUVRs than NCs in the overall age range.
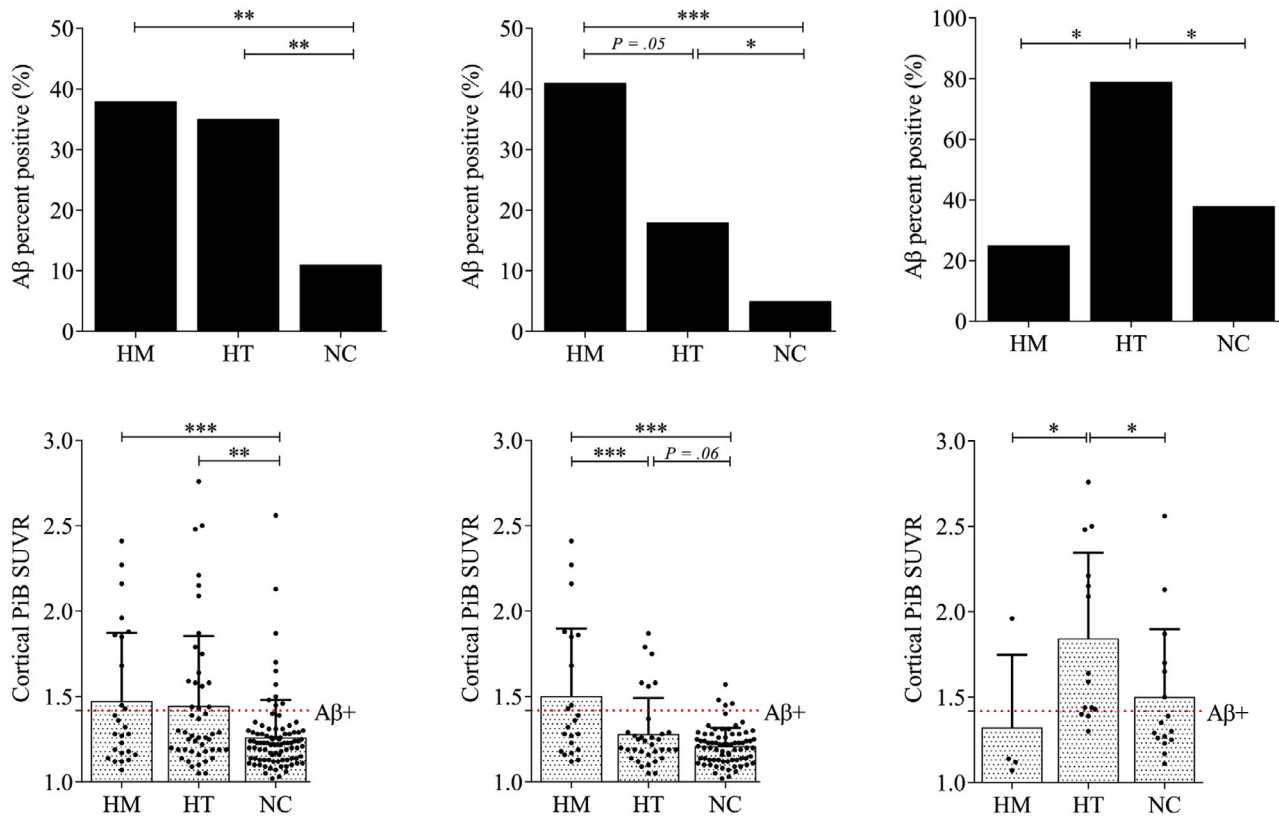
FIGURE 2 Relationships between Aβ plaque classification, measurements, and *APOE* ε4 gene dose in cognitively unimpaired participants age 47–86, 47–70, and 71–86 years. χ^2 tests were used to compare the proportions of Aβ positivity (top), and ANCOVA 2-tailed tests (adjusted for age, performance site, sex, and education) were used to compare cortical PiB SUVRs (bottom) in APOE ε4 HMs, HTs, and NCs. *,**,*** is $P < .05$, .01, and .001, respectively, for post hoc pairwise differences with Fisher's LSD. Means $\pm$ SD for cortical PiB SUVRs are shown (Aβ positivity threshold $\geq$1.42 is indicated with the red dotted line). Abbreviations: Aβ, amyloid β; ANCOVA, analysis of covariance; *APOE*, apolipoprotein E; HM, homozygote; HT, heterozygote; NC, noncarrier; SUVR, standard uptake value ratio.

PiB SUVRs were significantly higher in HM than in HT and NC, slightly higher in HT than in NC groups ($P = .06$), and were associated with *APOE* ε4 gene dose (linear trend, $P < .05$) in the younger age range. There were significantly higher cortical PiB SUVRs in HT than HM (who had relatively low SUVRs) and NC groups in the older age range.

2.3.7 | FTP PET measurements of tau/tangle burden

As shown in Table 4 and Fig. 3, ERC FTP SUVRs were significantly higher in HM and HT than NC groups in the overall age range; they were significantly higher in HM than HT (trend) and NC groups and associated with *APOE* ε4 gene dose in the younger age range (linear trend, $P < .05$); and they were significantly higher in HT than NC groups in the older age range. As shown in Fig. 3 and Supplementary Table 2, ERC FTP SUVRs were significantly higher in those with a positive Aβ PET scan and elevations in the HM and HT groups were attributable to those carriers with a positive Aβ PET scan.

As shown in Table 4 and Supplementary Tables 2, 3a and 3b, HT groups had significantly higher ITC and cortical tau SUVRs than NCs and were attributable to those HTs with a positive Aβ PET scan in the overall age range ($P < .05$). They were not significantly different

in HM, HT, and NC groups or associated with *APOE* ε4 gene dose in the younger age range. They were significantly higher in HT than NC groups in the older age range, but not solely attributable to the older HT group with a positive Aβ PET scan.

2.3.8 | MRI measurements of brain atrophy/neurodegeneration

As shown in Table 4, MRI measurements of cortical thickness and hippocampal gray matter volumes were not significantly different in the unimpaired HM, HT, and NC groups or associated with *APOE* ε4 gene dose in the overall, younger, or older age ranges and were significantly lower in older than younger participants, irrespective of *APOE* ε4 gene dose ($P \leq .01$, adjusted for site, sex, education, and *APOE status*).

3 | DISCUSSION

This study provides information about Aβ PET, tau PET, and volumetric MRI measurements, their associations with age, and A/T(N) classifications in a relatively large number of *APOE* ε4 HMs, HTs, and NCs,

TABLE 3 Classification of amyloid-β load (A), neurofibrillary tau burden (T), and neurodegeneration (N) in cognitively unimpaired *APOE ε4* HMs, HTs, and NCs

	(a) Ages 47–86				(b) Ages 47–70				(c) Ages 71–86			
	HMs, n = 26, %	HTs, n = 48, %	NCs, n = 90, %	P	HMs, n = 22, %	HTs, n = 34, %	NCs, n = 74, %	P	HMs, n = 4, %	HTs, n = 14, %	NCs, n = 16, %	P
A+T+(N)+	0	10	1	.01*	0	0	1	.68	0	36	0	.02¶
A+T+(N)−	12	10	2	.06†	9	3	0	.04*	25	29	13	.54
A+T−(N)−	27	13	6	.01‡	32	12	3	3e^{-4}§	0	14	19	.64
A+T−(N)+	0	2	2	.75	0	3	1	.67	0	0	6	.56
A−T+(N)+	0	0	2	.44	0	0	1	.69	0	0	6	.56
A−T+(N)−	8	6	14	.30	5	9	15	.36	25	0	13	.23
A−T−(N)+	8	8	9	.98	5	9	4	.57	25	7	31	.26
A−T−(N)−	46	50	63	.16	50	65	74	.09‖	25	14	13	.82

NOTE. Proportions were compared with a χ^2 test. *(a)* In the overall 47- to 86-year-old age range, higher proportion of HTs were A+T+(N)+ compared with NCs. A+T+(N)− nonsignificant trend, indicated significantly higher proportions of HMs and HTs compared with NCs. Post hoc pairwise comparisons of the nonsignificant trend in the A+T+(N)− indicated significantly higher proportions of HMs and HTs compared with NCs. Higher proportion of HMs were A+T−(N)− compared with NCs but not compared with HTs or between HTs and NCs. *(b)* In the younger 47- to 70-year-old age range, higher proportion of HMs were A+T+(N)− and A+T−(N)− compared with NCs, proportion of A+T−(N)− HMs were also slightly higher than in HTs and slightly higher in HTs than in NCs (nonsignificant). In the A−T−(N)−, differences in the proportions did not reach significance but the linear trend did (Mantel-Haenszel, P = .03), indicating an inverse association with *APOE ε4* gene dose (HM < HT < NC); post hoc pairwise comparisons were also significant with lower proportions of A−T−(N)− HMs compared with NCs but not with HTs or between HTs and NCs. *(c)* In the older 71- to 86-year-old age range, higher proportion of HTs were A+T+(N)+ compared with NCs but did not reach significance compared with HMs. χ^2 P values and percent listed.
Abbreviations: Aβ, amyloid β; *APOE*, apolipoprotein E; HM, homozygote; HT, heterozygote; NC, noncarrier.
*HT > NC
†HM & HT > NC
‡HM > NC (P < .05)
§HM > HT & NC
‖HM < NC (P ≤ .06)
¶HT > NC (P ≤ .01)

TABLE 4 Brain imaging measurements of Aβ plaque burden, tau/tangle burden, and atrophy/neurodegeneration in cognitively unimpaired *APOE ε4* HMs, HTs, and NCs

	(a) Ages 47–86				(b) Ages 47–70				(c) Ages 71–86			
	HMs, n = 26	HTs, n = 48	NCs, n = 90	P	HMs, n = 22	HTs, n = 34	NCs, n = 74	P	HMs, n = 4	HTs, n = 14	NCs, n = 16	P
Cortical PiB SUVR	1.50 ± .06	1.43 ± .04	1.26 ± .03	1e^{-4}*	1.51 ± .04	1.28 ± .03	1.21 ± .02	1e^{-8}§	1.09 ± .28	1.95 ± .12	1.47 ± .11	.01#
ERC FTP SUVR	1.12 ± .02	1.12 ± .02	1.05 ± .02	.02*	1.10 ± .02	1.04 ± .02	1.03 ± .01	.04¶	1.07 ± 1.0	1.23 ± .04	1.07 ± .04	.03†
ITC FTP SUVR	1.19 ± .02	1.21 ± .02	1.18 ± .02	.10†	1.17 ± .02	1.17 ± .02	1.17 ± .01	.99	1.21 ± .09	1.35 ± .04	1.22 ± .04	.07†
Cortical tau FTP SUVR	1.17 ± .02	1.20 ± .01	1.16 ± .02	.10‡	1.15 ± .02	1.14 ± .01	1.14 ± .01	.89	1.19 ± .08	1.32 ± .04	1.20 ± .04	.05‡
Cortical thickness	2.78 ± .02	2.76 ± .02	2.79 ± .01	.21	2.80 ± .02	2.78 ± .02	2.80 ± .01	.47	2.68 ± .08	2.70 ± .04	2.74 ± .04	.67
Hippocampal volume	0.53 ± .01	0.53 ± .01	0.54 ± .01	.40	0.54 ± .01	.54 ± .01	0.55 ± .01	.93	0.48 ± .04	0.49 ± .01	0.51 ± .02	.65

NOTE. ANCOVA 2-tailed tests, adjusted for age, performance site, sex, and education were used to compare brain imaging measurements in (a) 47–86, (b) 47–70, and (c) 71–86 year-old age ranges. Aβ positivity was used as an interaction term in the overall 47–86 age range [*APOE ε4* group*Aβ-status (Aβ+/Aβ−)] for tau PET and MRI measures. Mean SUVR ± SE, and significant (P < .05) and nonsignificant trends (P values between .05 and .10) with pairwise differences using Fisher's LSD, are listed.
Abbreviations: Aβ, amyloid β; ANCOVA, analysis of covariance; *APOE*, apolipoprotein E; ERC, entorhinal cortex; FTP, flortaucipir; HM, homozygote; HT, heterozygote; ITC, inferior temporal cortex; NC, noncarrier; SUVR, standard uptake value ratio.
*HM & HT > NC
†HT > NC
‡HT > NC (P < .05)
§HM > HT > NC
¶HM > HT & NC (P ≤ .06)
#HT > HM & NC

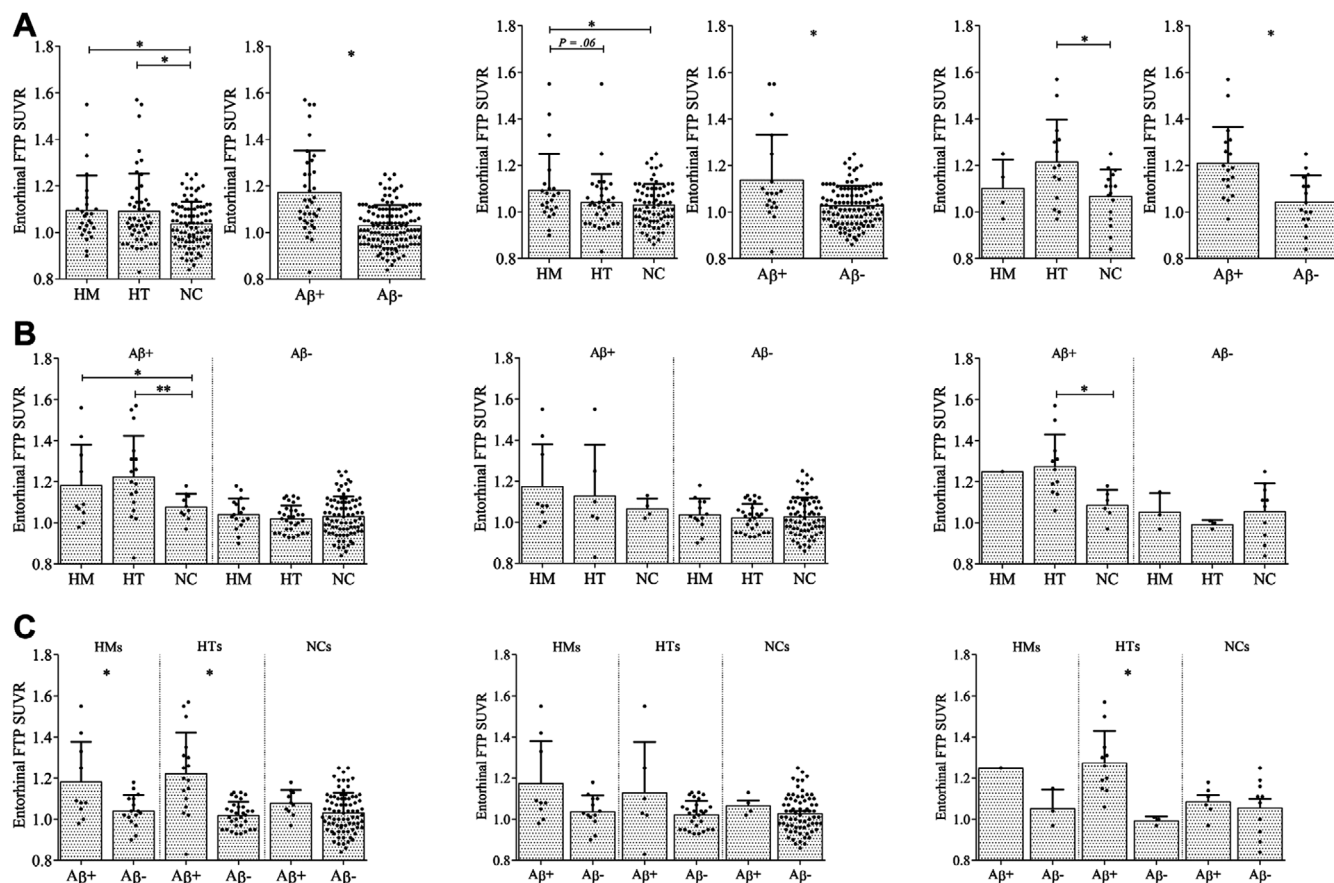**FIGURE 3** Relationships between entorhinal tau deposition, Aβ positivity, and *APOE ε4* gene dose in cognitively unimpaired participants at age 47–86, 47–70, and 71–86 years. ANCOVA 2-tailed tests (adjusted for age, performance site, sex, and education) were used to compare *(a)* entorhinal FTP SUVRs in APOE ε4 HMs, HTs and NCs, and in Aβ-positive (Aβ+) vs Aβ-negative (Aβ-) participants. *(b-c)* Aβ positivity was used as an interaction term in the overall 47–86 age range [APOE ε4 group*Aβ status (Aβ+/Aβ−)] and ran separately in the Aβ+ and Aβ− 47- to 70-year-old and 71- to 86-year-old subgroups. * is *P* < .05 for post hoc pairwise differences with Fisher's LSD and means ± SD are shown. Abbreviations: Aβ, amyloid β; ANCOVA, analysis of covariance; *APOE*, apolipoprotein E; HM, homozygote; HT, heterozygote; NC, noncarrier; FTP, flortaucipir; SUVR, standard uptake value ratio.

and over a relatively large middle-to-older age range. Aβ and ERC tau PET measurements rose, plateaued, and declined with age in the unimpaired HM and HT groups and did so earlier in HMs than HTs. ERC tau PET measurements were significantly greater in the HM and HT groups, and these elevations were attributable to those carriers with a positive Aβ PET scans. Together, our findings suggest that cognitively unimpaired HMs can be studied before their 70s to evaluate biomarker changes, risk factors, pathophysiological changes, and interventions involved in the *predisposition* to and potential prevention of AD. Although our study included only four unimpaired HMs aged over 70 years, our findings suggest that HMs who remain cognitively unimpaired after their 70s could be used to evaluate biomarker changes, risk factors, pathophysiological changes, and interventions involved in the *resilience or resistance* to and prevention of AD.

In the cognitively unimpaired *APOE ε4* HM group, cortical Aβ PET measurements rose with age, were significantly different from those in NC group by age 62, plateaued at age 68, declined, and were no longer significantly different from NCs by age 71. ERC tau PET measurements

rose with age, were significantly different from those in the NC groups by age 66, plateaued at age 71, declined, and were no longer significantly different from NCs by age 74. The HT group demonstrated a similar pattern of Aβ and ERC tau PET increases, plateaus, and declines occurring about 4-8 years later. We reason that the decline in prevalence among HM and HT groups is not due to decline in levels of protein deposition in the brains of individuals over time, but rather it is a drop in the group mean due to selective survival of resilient low amyloid and low tau individuals at older ages.

We hypothesize that subsequent biomarker declines are attributable to resistance factors that permit HMs and HTs to remain cognitively unimpaired at older ages.[27] Although retrospective case-control studies indicate that *APOE ε4* gene dose is associated with very high AD dementia odds ratios, prospective cohort studies support the possibility that there are a greater number of *APOE ε4* HMs and HTs who remain cognitively unimpaired at older ages—individuals who could help clarify the factors that account for resilience or resistance to the clinical onset of AD. Although studies have provided information

about when the risk of AD dementia begins to rise, plateau, and decline in HM and HT groups, our study provides information about the ages at which brain imaging biomarkers of Aβ plaque and tau/tangle deposition begins to rise, plateau, and decline.

We hypothesize that cognitively unimpaired HM and HT groups could be studied before their 70s, when their biomarker changes are associated with three levels of genetic risk, for the following purposes: 1) to clarify the impact of genetic and nongenetic risk factors and their interaction with APOE ε4 gene dose, on AD biomarkers (or "endophenotypes"), as we have done in the past using a more limited number of biomarker measurements[10,19,38] and 2) to evaluate promising prevention therapies before AD is extensive, including those who have or have not yet have biomarker evidence of amyloid burden, as we are doing in the Alzheimer's Prevention Initiative Generation Program.[39–41]

We hypothesize that cognitively unimpaired HM and HT groups who remain unimpaired at older ages could be used to investigate the impact of putative protective factors and clarify differential effects of these protective factors on Aβ or downstream neuroinflammatory, tau, or neurodegeneration biomarkers. This information could help provide new targets at which to aim promising prevention therapies.

In addition to the associations of biomarker changes with age in unimpaired HMs, HTs, and NCs, our study provides other insights about biomarker changes and classifications in these groups. For instance, it suggests that ERC tau PET elevations in HM and HT groups are attributable to those with a positive Aβ PET scan. Although one cannot draw strong conclusions about the causal connection between Aβ and tau PET measurements in these at risk groups, this finding does support the possibility that treatments that prevent the initial accumulation of neuritic plaques might reduce the development of downstream neuropathological changes and ensuing cognitive decline—a possibility that is now being explored in the subset of cognitively unimpaired 60- to 75-year-old HMs that are being evaluated using an anti-amyloid immunotherapy in the Alzheimer's Prevention Initiative Generation Program.

In our effort to classify the three genetic groups based on criteria for a "positive" or "negative" Aβ PET, tau PET, and volumetric MRI findings, we found a surprisingly low percentage of HMs who were neurodegeneration positive, and we did not see a strong association between tau PET measurements and APOE ε4 gene dose in ITC and cortical regions that have been suggested to help distinguish between AD cases and controls. These "negative" findings could be attributable to several factors, such as a relatively brief interval between neurodegeneration positivity and clinical progression, exclusion of those who had already progressed, resilience or resistance factors in the small number of those HMs who remained unimpaired at older ages, and/or cortical tau and cortical atrophy thresholds used to define positivity. Additional image analysis techniques and thresholds may be needed to define tau and neurodegeneration positivity in the preclinical stages of AD. These thresholds could then be evaluated in terms of their prognostic value, their diagnostic value (including their correspondence to postmortem neuropathology), and their predictive value (i.e., their ability to inform the differential response to treatment). We do note, however, that there is an APOE ε4 gene dose effect (i.e., HM > HT > NC,

linear trend) when we compare the proportions of A+T+ (irrespective of N) or A+T−N− HM, HT, and NC groups in the overall and younger age ranges.

Finally, recent studies report biomarker effects on memory performance, particularly with ERC tau deposition in cognitively unimpaired participants[33,34] however, APOE ε4 effects on memory performance in the present study are not as clear and will likely require more than one memory measurement and a larger sample to properly assess. Despite some of these limitations, we note significantly higher long-term recall memory scores in the older HMs than in HTs and NC groups (Table 1), suggesting that resilience or resistance to cognitive decline in the small older HM group may not be solely attributable to education-related cognitive reserve. We also see lower MMSE and long-term recall scores in Aβ-positive participants relative to Aβ negative for the overall and younger age ranges (Supplementary Table 2).

Strengths of this study include the relatively large number of cognitively unimpaired APOE ε4 HMs and age-, sex-, and education-matched HTs and NCs with PiB PET, FTP PET, and volumetric MRI, and the nearly 40-year age range, which permitted us to characterize associations with age, some information from the longitudinal Arizona APOE Cohort to help inform the impact of differential survivor bias on our findings, and the opportunity afforded by differential survivor bias to help in the study of resilience or resistance at older ages. Limitations include the size of the APOE ε4 HM group, particularly at older ages, the differential survivor bias described previously (including likely affected age estimates and the absence of Aβ PET, tau PET, and MRI data from participants after their clinical progression), differences between the participants and measurements included in the two cohorts, and the absence of longitudinal data to go beyond the study of age associations to the characterization of trajectories.

4 | CONCLUSIONS

This study provides information about Aβ plaque burden, tau-tangle burden, and neurodegeneration in cognitively unimpaired persons at three levels of genetic risk for AD. We suggest that unimpaired APOE ε4 HMs can be studied before their 70s to clarify the biomarker changes, risk factors, pathophysiological processes, and interventions involved in the *predisposition* to and prevention of AD and after their 70s to clarify the biomarker factors, risk modifiers, pathophysiological processes, therapeutic targets, and interventions involved in the *resilience or resistance* to and prevention of AD.

REFERENCES

1. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's Dement*. 2012;8:1-13.
2. Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol*. 2012;123:1-11.
3. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82:239-259.
4. Thal DR, Rüb U, Orantes M, Braak H. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. *Neurology*. 2002;58:1791-1800.
5. Braak H, Alafazoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol*. 2006;112:389-404.
6. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261:921-923.
7. Coon KD, Myers AJ, Craig DW, Webster JA, Pearson JV, Lince DH, et al. A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. *J Clin Psychiat*. 2007;68:613-618.
8. Bondi MW, Salmon DP, Galasko D, Thomas RG, Thal LJ. Neuropsychological function and apolipoprotein E genotype in the preclinical detection of Alzheimer's disease. *Psychol Aging*. 1999;14:295-303.
9. Lange KL, Bondi MW, Salmon DP, Galasko D, Delis DC, Thomas RG, et al. Decline in verbal memory during preclinical Alzheimer's disease: examination of the effect of APOE genotype. *J Int Neuropsychol Soc*. 2002;8:943-955.
10. Reiman EM, Chen K, Liu X, Bandy D, Yu M, Lee W, et al. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2009;106:6820-6825.
11. Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, et al. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. *N Engl J Med*. 2009;361:255-263.
12. Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. 2015;313:1924-1938.
13. Coughlan G, Coutrot A, Khondoker M, Minihane AM, Spiers H, Hornberger M. Toward personalized cognitive diagnostics of at-genetic-risk Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2019;116:9285-9292.
14. Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med*. 1996;334:752-758.
15. Reiman EM, Caselli RJ, Alexander GE, Chen K. Tracking the decline in cerebral glucose metabolism in persons and laboratory animals at genetic risk for Alzheimer's disease. *Clin Neurosci Res*. 2001;1:194-206.
16. Reiman EM, Caselli RJ, Chen K, Alexander GE, Bandy D, Frost J. Declining brain activity in cognitively normal apolipoprotein E epsilon 4 heterozygotes: A foundation for using positron emission tomography to efficiently test treatments to prevent Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2001;98:3334-3339.
17. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, et al. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc Natl Acad Sci U S A*. 2004;101:284-289.
18. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, et al. Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. *Proc Natl Acad Sci U S A*. 2005;102:8299-8302.
19. Reiman EM, Chen K, Caselli RJ, Alexander GE, Bandy D, Adamson JL, et al. Cholesterol-related genetic risk scores are associated with hypometabolism in Alzheimer's-affected brain regions. *Neuroimage*. 2008;40:1214-1221.

20. Reiman EM, Chen K, Langbaum JB, Lee W, Reschke C, Bandy D, et al. Higher serum total cholesterol levels in late middle age are associated with glucose hypometabolism in brain regions affected by Alzheimer's disease and normal aging. *Neuroimage.* 2010;49:169-176.

21. Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology.* 2008;30:58-69.

22. Petersen RC, Wiste HJ, Weigand SD, Rocca WA, Roberts RO, Mielke MM, et al. Association of Elevated Amyloid Levels With Cognition and Biomarkers in Cognitively Normal People From the Community. *JAMA Neurol.* 2016;73:85-92.

23. Jack CR Jr., Wiste HJ, Weigand SD, Therneau TM, Knopman DS, Lowe V, et al. Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50–95 years: a cross-sectional study. *The Lancet Neurol.* 2017;16:435-444.

24. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease - A meta-analysis. *JAMA.* 1997;278:1349-1356.

25. Meyer MR, Tschanz JT, Norton MC, Welsh-Bohmer KA, Steffens DC, Wyse BW, et al. APOE genotype predicts when--not whether--one is predisposed to develop Alzheimer disease. *Nat Genet.* 1998;19:321-322.

26. Breitner JC, Wyse BW, Anthony JC, Welsh-Bohmer KA, Steffens DC, Norton MC, et al. APOE- 4 count predicts age when prevalence of AD increases, then declines. *Neurology.* 2000;55:161-162.

27. Arenaza-Urquijo EM, Vemuri P. Resistance vs resilience to Alzheimer disease: Clarifying terminology for preclinical studies. *Neurology.* 2018;90:695-703.

28. Jack CR Jr., Wiste HJ, Weigand SD, Therneau TM, Lowe VJ, Knopman DS, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. Alzheimer's & dementia. *J Alzheimer's Assoc.* 2017;13:205-216.

29. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res.* 1990;31:545-548.

30. Crook R, Hardy J, Duff K. Single-day apolipoprotein E genotyping. *J Neurosci Methods.* 1994;53:125-127.

31. Iturria-Medina Y, Sotero RC, Toussaint PJ, Evans ACAlzheimer's Disease Neuroimaging Initiative. Epidemic spreading model to characterize misfolded proteins propagation in aging and associated neurodegenerative disorders. *Plos Comput Biol.* 2014;10:e1003956.

32. Quiroz YT, Sperling RA, Norton DJ, Baena A, Arboleda-Velasquez JF, Cosio D, et al. Association Between Amyloid and Tau Accumulation in Young Adults With Autosomal Dominant Alzheimer Disease. *JAMA Neurol.* 2018;75:548-556.

33. Knopman DS, Lundt ES, Therneau TM, Vemuri P, Lowe VJ, Kantarci K, et al. Entorhinal cortex tau, amyloid-beta, cortical thickness and memory performance in non-demented subjects. *Brain.* 2019;142:1148-1160.

34. Lowe VJ, Bruinsma TJ, Wiste HJ, Min HK, Weigand SD, Fang P, et al. Cross-sectional associations of tau-PET signal with cognition in cognitively unimpaired adults. *Neurology.* 2019;93:e29-e39.

35. Jack CR Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's Dement.* 2018;14:535-562.

36. Fox J, Weisberg S. An R companion to applied regression. 2018; Sage Publications.

37. Qian J, Wolters FJ, Beiser A, Haan M, Ikram MA, Karlawish J, et al. APOE-related risk of mild cognitive impairment and dementia for prevention trials: An analysis of four cohorts. *Plos Med.* 2017;14:e1002254.

38. Langbaum JB, Chen K, Launer LJ, Fleisher AS, Lee W, Liu X, et al. Blood pressure is associated with higher brain amyloid burden and lower glucose metabolism in healthy late middle-age persons. *Neurobiol Aging.* 2012;33:827.e11-827.e19.

39. Reiman EM. Alzheimer disease in 2016: Putting AD treatments and biomarkers to the test. *Nat Rev Neurol.* 2017;13:74-76.

40. Reiman EM, Langbaum JB, Tariot PN, Lopera F, Bateman RJ, Morris JC, et al. CAP--advancing the evaluation of preclinical Alzheimer disease treatments. *Nat Rev Neurol.* 2016;12:56-61.

41. Reiman EM, Langbaum JB, Fleisher AS, Caselli RJ, Chen K, Ayutyanont N, et al. Alzheimer's Prevention Initiative: a plan to accelerate the evaluation of presymptomatic treatments. *J Alzheimers Dis.* 2011;26:321-329.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.